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Claims

1. Process for the preparation of roflumilast by reacting the anion of 4-amino-3,5-dichloropyridine (1)

in which A⁺ is a cation, preferably an alkali metal cation and particularly preferably a potassium cation, with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2),

In which LG is a suitable leaving group, preferably a chlorine atom, a bromine atom or a radical of the formula OC(O)-1-4C-alkyl, and particularly preferably a chlorine atom, characterized in that the molar ratio of the employed anion of 4-amino-3,5-dichloropyridine (1) to the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is at least 1.5 and at most 3.

- 2. Process according to Claim 1, characterized in that the molar ratio of the employed anion of 4-amino-3,5-dichloropyridine (1) to the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxy-benzolc acid (2) is at least 1.8 and at most 2.7.
- 3. Process according to Claim 1, characterized in that the molar ratio of the employed anion of 4-amino-3,5-dichloropyridine (1) to the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxy-benzolc acid (2) is at least 2 and at most 2.5.

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- 4. Process according to Claim 1, characterized in that the molar ratio of the employed anion of 4-amino-3,5-dichloropyridine (1) to the activated derivative of 3-cyclopropylmethoxy-4-diffuoromethoxy-benzoic acid (2) is 2.2.
- 5. Process according to any of Claims 1 to 4, characterized in that the reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is carried out in a solvent selected from the group of dichloromethane, toluene, xylene, dimethylformamide or N-methylpyrrolidone.
- 6. Process according to any of Claims 1 to 4, characterized in that the reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is carried out in a dimethylformamide.
- 7. Process according to any of Claims 1 to 6, characterized in that the reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-diffuoromethoxybenzoic acid (2) is carried out a temperature between 0°C and the boiling point of the inert solvent used.
- 8. Process according to any of Claims 1 to 6, characterized in that the reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is carried out a temperature between 20 °C and 30 °C
- Process according to any of Claims 1 to 8, characterized in that the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzolc acid (2) is 3-cyclopropylmethoxy-4-difluoromethoxybenzolc cloride.
- Process according to any of Claims 1 to 8, characterized in that the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is 3-cyclopropylmethoxy-4-difluoromethoxybenzoyl bromide.
- 11. Process according to any of Claims 1 to 8, characterized in that the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is a 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid 1-4C-alkyl-ester.
- 12. Process according to any of Claims 1 to 11, characterized in that a strong base selected from the group of KOtBu, NaOtBu and LiOtBu is used to prepare the anion of 4-amino-3,5-dichloropyridine.

- 13. Process according to Claim 12, characterized in that KOtBu is used to prepare the anion of 4-amino-3,5-dichloropyridine (1).
- 14. Process according to any of Claims 1 to 13, characterized in that the product resulting from the process is recrystallized in a mixture of isopropanol and water (ratio isopropanol/water: between 85:15 and 100:0% by volume, preferably between 90:10 and 95:5% by volume).
- 15. Roflumilast prepared by a process according to any of Claims 1 to 14.
- 16. Röflumilast prepared by a process according to any of Claims 1 to 14, characterized in that the purity is ≥ 99% by weight, preferably ≥ 99.8% by weight.
- 17. Roflumilast prepared by a process according to any of Claims 1 to 14, characterized in that it contains less than 0.1% by weight, preferably less than 0.05% by weight, of the by-product N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-hydroxybenzamide.
- 18. Roflumilast prepared according to Claim 15, 16 or 17 for use in the treatment of diseases.
- 19. Pharmaceutical compositions containing roflumilast prepared according to Claim 15, 16 or 17 together with conventional pharmaceutical auxiliaries and/or excipients.
- 20. Use of the roflumlast prepared according to Claim 15, 16 or 17 for the production of pharmaceutical compositions for the treatment of an acute or chronic airway disorder, a dermatosis or an arthritic disorder.
- 21. Method for the treatment of mammals, including humans, suffering from an acute or chronic airway disorder, a dermatosis or an arthritic disorder, characterized in that a therapeutically effective amount of the roflumilast prepared according to Claim 15, 16 or 17 is administered together with conventional auxiliaries and/or excipients to the mammal with the disorder.